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09/886,313	06/21/2001	Alexander Michael Chagovetz	46641-01010	5607

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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,313	CHAGOVETZ, ALEXANDER MICHAEL	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17 and 20-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17, 20-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on January 8, 2004 has been entered.

2. Claims 1-16 and 18-19 are cancelled. Claim 17 is amended. New claims 20-54 are added. Claims 17, and 20-54 are pending.

3. This application is filed on June 21, 2001.

Response to Arguments

4. Applicants' response to the office action is fully considered and found persuasive in part.

5. With regard to the rejections made in the previous office action under 35 USC 112, second paragraph, applicants' amendment and arguments are fully considered and the rejections are withdrawn in view of the amendment.

6. With regard to the rejection made in the previous office action under 35 USC 102(e), applicants' amendment and arguments are fully considered. The rejection is withdrawn in view of cancellation of claims 1-16 and new grounds of rejection. Applicants' arguments are fully considered and found not persuasive. Applicants' argue that Nazeranko et al. teach hairpin primers and not linear primers each labeled with a flurophore and triamplification . These arguments are fully considered and found not persuasive because Nazarenko et al. teach both hairpin and linear primers for PCR amplification and also teach standard PCR amplification in addition to the method of triamplification. Further the instant claims do not exclude the use of hairpin primers since the limitation "not using hairpin primers" is not present in the instant claims. Nazarenko et al. reference is still deemed as a prior art for the newly added claims and the rejection is written below addressing the newly added claims.

7. With regard to the rejection made in the previous office action under 35 USC 103(a), Applicants' arguments are fully considered and are persuasive. The rejection is withdrawn in view of arguments and new grounds of rejections.

New Rejections

8. The instant specification is objected because of the following informalities:

(i) in the new claim 21, step (d) 'produce' is misspelled as 'product'. Correction is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

A. Claim 17, 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Shriver et al. (USPN.6,506,568).

Shriver et al. teach a method of claim 17, for detecting a nucleic acid target sequence in a sample, comprising

(a) obtaining a sample of nucleic acid material to be analyzed (see column 3, lines 10-13, column 6, lines 1-2);

(b) selecting a nucleic acid target sequence having a length of up to 130 nucleotides expected to be found in said nucleic acid material (see column 3, lines 10-13 for DNA comprising selected SNP target, and, see column 8, lines 21-32, for the expected length of the selected target sequence);

(c) synthesizing a primer pair (forward and reverse) for amplifying said target sequence in polymerase chain reaction to produce a double stranded amplification product (see column 6, lines 2-7, column 8, lines 21-24);

(d) preparing a dye (SYBR Green I or II) for labeling a double-stranded amplification product in solution when such amplification product is formed said dye being detectable by a fluorimetric measuring device (melting curve analysis-LightCycler) (see column 3, lines 50-55);

(e) introducing a quantity of said forward and reverse primers, a quantity of deoxynucleotide triphosphates, a quantity of said dye, and a quantity of said nucleic acid material in an aqueous medium (see column 3, lines 32-37, column 6, lines 22-28);

(f) inducing an amplification reaction, producing a labeled double-stranded amplification product derived from said target sequence labeled by said dye (see column 3, lines 20-37, column 6, lines 15-28);

(g) detecting said labeled amplification product by detecting said dye with said fluorimetric device (see column 3, lines 50-55, column 17, lines 15-46, column 18, lines 1-12).

With regard to claim 20, Shriver et al. disclose that said nucleic acid target sequence has a length rang from about 25 nucleotides to about 100 nucleotides (see column 8, lines 21-32, column 14, lines 59-64). Thus the disclosure of Shriver et al. meets the limitations in the instant claims.

B. Claims 21-30, 35-36, 38-41, 44-49, 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Nazarenko et al. (USPN. 5,866,336).

With reference to the instant claims 21, Nazarenko et al. teach a method for detecting a nucleic acid target sequence in a sample wherein Nazarenko et al. disclose that the method comprises (a-b) obtaining and selecting a nucleic acid target sequence in a target sample (see column 38, lines 27-36); (c-f) synthesizing a primer pair (linear primers) for amplifying said target sequence in a polymerase chain reaction wherein the forward and reverse primers and providing first and second dyes for labeling said primers (see column 23, lines 12-38); (g) introducing a quantity of said forward and reverse primers , a quantity of Taq polymerase, dNTPs, and a quantity of said target sequence in an aqueous reaction medium, in a reaction vessel (see column 38, lines 37-41, column 29, lines 50-67, column 30, lines 1-19); (h) initiating the polymerase chain reaction, producing a double stranded amplification product, wherein the amplification reaction comprises incorporated primers producing a signal upon energy stimulus and detecting the signal using gel electrophoresis and spectroflurophotometer (see column 38, lines 55-63).

With reference to the instant claims 22-24, 28, 34, Nazarenko et al. also discloses that the method comprises (i) first and second dyes as fluorescent dyes including phosphorescent dye

moieties and luminescent dye moieties and signal involves fluorescent resonance energy transfer (FRET) (see column 18, lines 29-67, table.1);

With reference to claims 25, Nazarenko et al. disclose said nucleic acid includes double-stranded DNA (see column 38, lines 37-41);

With reference to claims 26-27, Nazarenko et al. disclose said nucleic acid polymerase is a Taq or Pfu polymerase (see column 38, lines 40-41, column 42, lines 22-41);

With reference to claims 29, Nazarenko et al. disclose said specific proximity of FRET moieties are separated by up to 30 nucleotides (about 100 A^0) (see column 18, lines 43-59);

With reference to claims 30, Nazarenko et al. disclose said measuring device is a spectroflurimeter (see column 38, lines 55-63);

With reference to claims 35, Nazarenko et al. disclose said control reaction comprises no DNA (see column 44, lines 5-16);

With reference to claims 36, Nazarenko et al. disclose applying external energy stimulus (at particular wave length excitation) and monitoring the intensity of the signal to determine the concentration of said amplification product (column 38, lines 55-63, column 44, lines 5-16, table.2);

With reference to claims 38, Nazarenko et al. disclose said sample of nucleic acid includes mRNA and wherein the step of initiating PCR includes cDNA (see column 38, lines 27-36);

With reference to claims 39, Nazarenko et al. disclose said signal is analyzed to determine the length of said target sequence (see column 49, lines 1-6);

With regard to claim 40, 45-46, 52, Nazarenko et al. also teach detecting more than one target nucleic acid sequences using two or more pairs of primers (see column 30, lines 63-67, column 31, lines 1-12);

With reference to claims 41, 44, 47-49, 52, Nazarenko et al. disclose target sequence includes a mutation point, primers are designed to flank the mutation point and amplification product includes a copy of said mutation point (column 25, lines 22-40);

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-33, 37, 42-43, 50-51, 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al. (USPN.5,866,336) in view of Shriver et al. (USPN. 6,506,568).

Nazarenko et al. teach a method for detecting a nucleic acid target sequence in a sample wherein Nazarenko et al. disclose that the method comprises (a-b) obtaining and selecting a nucleic acid target sequence in a target sample (see column 38, lines 27-36); (c-f) synthesizing a primer pair (linear primers) for amplifying said target sequence in a polymerase chain reaction wherein the forward and reverse primers and providing first and second dyes for labeling said primers (see column 23, lines 12-38); (g) introducing a quantity of said forward and reverse primers , a quantity of Taq polymerase, dNTPs, and a quantity of said target sequence in an

aqueous reaction medium, in a reaction vessel (see column 38, lines 37-41, column 29, lines 50-67, column 30, lines 1-19); (h) initiating the polymerase chain reaction, producing a double stranded amplification product, wherein the amplification reaction comprises incorporated primers producing a signal upon energy stimulus and detecting the signal using gel electrophoresis and spectroflurophotometer (see column 38, lines 55-63).

Nazarenko et al. also discloses that the method comprises (i) first and second dyes as fluorescent dyes including phosphorescent dye moieties and luminescent dye moieties and signal involves fluorescent resonance energy transfer (FRET) (see column 18, lines 29-67, table.1); applying external energy stimulus (at particular wave length excitation) and monitoring the intensity of the signal to determine the concentration of said amplification product (column 38, lines 55-63, column 44, lines 5-16, table.2); detecting more than one target nucleic acid sequences using two or more pairs of primers (see column 30, lines 63-67, column 31, lines 1-12); and target sequence includes a mutation point, primers are designed to flank the mutation point and amplification product includes a copy of said mutation point (column 25, lines 22-40). However, Nazarenko et al. did not specifically teach a target sequence having a length up to 130 nucleotides in length, detection of signal using melting analysis and monitoring the signals.

Shriver et al. teach a method of claim 17, for detecting a nucleic acid target sequence in a sample, comprising

(a) obtaining a sample of nucleic acid material to be analyzed (see column 3, lines 10-13, column 6, lines 1-2);

(b) selecting a nucleic acid target sequence having a length of up to 130 nucleotides expected to be found in said nucleic acid material (see column 3, lines 10-13 for DNA

comprising selected SNP target, and, see column 8, lines 21-32, for the expected length of the selected target sequence);

(c) synthesizing a primer pair (forward and reverse) for amplifying said target sequence in polymerase chain reaction to produce a double stranded amplification product (see column 6, lines 2-7, column 8, lines 21-24);

(d) preparing a dye (SYBR Green I or II) for labeling a double-stranded amplification product in solution when such amplification product is formed said dye being detectable by a fluorimetric measuring device (melting curve analysis-LightCycler) (see column 3, lines 50-55);

(e) introducing a quantity of said forward and reverse primers, a quantity of deoxynucleotide triphosphates, a quantity of said dye, and a quantity of said nucleic acid material in an aqueous medium (see column 3, lines 32-37, column 6, lines 22-28);

(f) inducing an amplification reaction, producing a labeled double-stranded amplification product derived from said target sequence labeled by said dye (see column 3, lines 20-37, column 6, lines 15-28);

(g) detecting said labeled amplification product by detecting said dye with said fluorimetric device (see column 3, lines 50-55, column 17, lines 15-46, column 18, lines 1-12).

Shriver et al. also disclose that said nucleic acid target sequence has a length rang from about 25 nucleotides to about 100 nucleotides (see column 8, lines 21-32, column 14, lines 59-64); use of second fluorescent dye in addition to the FRET moieties and multiple flurophore dyes are simultaneously monitored (see column 12, lines 9-43).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method for detection of a target nucleic acid

sequence as taught by Nazarenko et al., with the selection of the length of the target nucleic acid sequence and melting curve analysis as taught by Shriver et al. to achieve expected advantage of developing an improved sensitive method for detecting a target nucleic acid sequence because Shriver et al. taught that (i) selection of a nucleic acid target of about 50-150 base pairs in length (small amplicons) would work well with a wide variety of the PCR conditions, (ii) the size and sequence of the amplicons are the two most important factors in melting curve analysis (see column 8, lines 25-32, column 14, lines 59-64). Thus an ordinary practitioner would have been motivated to combine the method for detecting a target nucleic acid sequence as taught by Nazarenko et al. with the inclusion of the size and sequence limitations as taught by Shriver et al. which would result in developing an improved and sensitive method for detecting the target nucleic acid sequences with more sensitive instruments which would reduce background signal/noise ratio.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
April 15, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER